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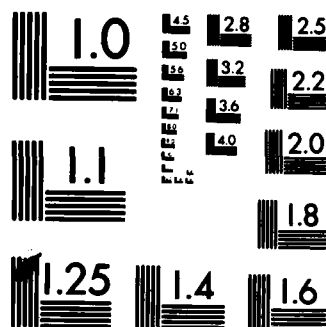
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FINAL REPORT

World Reference Center and Arbovirus Diagnosis

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Introduction. The World Reference Center for Arboviruses was established at the Yale Arbovirus Research Unit in 1965 as an outgrowth of The Rockefeller Foundation program on arboviruses which was moved in 1965 to Yale University from New York City. The U.S. Navy has supported this program since 1972, initially through joint Navy-Army funding, then through a separate contract. In April, 1977, the Yale Arbovirus Research Unit became the billet of a Navy officer and has since remained the billet of one or two officers. The present contract was initiated in 1977. The progress over these six years is included in this report; it covers the work for the entire project which received support from the Army, WHO, NIH, and Australian government, in addition to that of this contract.

Virus identification. A primary function of the reference center is to receive viruses from all parts of the world for identification. The most resounding identifications were bluetongue virus from Australia and Rift Valley fever virus from Egypt in 1977. Details of these and other identifications are given in Status Reports and Annual Reports from 1977 to 1983. New viruses identified included Aroa virus from Venezuela and Tamana virus from bats in Trinidad, both new flaviviruses, as well as other new flaviviruses from Australia, and France. Twenty-seven new viruses from Brazil were identified. Among them was a new Anopheles A group virus; 2 new ungrouped viruses from Sabethes and from Aedes mosquitoes; a new flavivirus; 4 new ungrouped viruses in the Bunyamwera group from Sabethes and Wyeomyia mosquitoes and a bat; a new bunyavirus from a sentinel mouse; 4 new phleboviruses — one from a spiny rat and 3 from sandflies; 2 new rhabdoviruses from a lizard and a toad and a new vesiculovirus from male sandflies; a new Bunyamwera group virus from a fatal case of hepatitis; 5 new Changuinola group viruses from a sloth, an armadillo, and sandflies respectively; 2 new Corriparta group viruses from mosquitoes; a new Pacora group virus from a bird; and a new Bunyamwera supergroup virus from a bat. A new Yogue group virus was recognized from febrile patients and from bats in Uganda, and a new Ornithodoros virus and a new Tete group virus from India. Tilligery was a new Eubenangae group orbivirus from Australia. Other new viruses included the orbivirus, GG668, the tick bunyavirus MI 19334, Termeil, Yacaaba, and PK886 viruses from mosquitoes, CSIRO-25 virus from Culicoides, and a new virus from Argas ticks — all isolated in Australia; a new virus from Tanzanian Argas, a new virus from Ornithodoros ticks collected in the U.S., and Connecticut virus, a new rhabdovirus from ticks in New England.

Previously described viruses were identified from new geographic regions, including Thogoto from ticks, Sango from Culicoides, Dugbe from birds, Arumowot from rodents, and Germiston from sentinel mice — all from Ethiopia; Umbre and Thimiri for the first time in Australia; Arumowot from South Africa; Wad Medani, Wanowrie, and Quarafil from Iran; Soldado Rock virus from France and the Seychelles; Chenuda virus in Morocco; Tataguine virus from the Gambia; Kemerovo group viruses from the U.K., Finland, and France; Salehabad, a Sakhalin group virus and Eyach virus from France, a Kemerovo group virus recovered from anal swabs of Thai bats, Sindbis from bats of Zimbabwe, and Tyuleniy from ticks of the North Atlantic. Crimean-Congo hemorrhagic fever virus was confirmed from China. Rift Valley fever (Zinga) virus was recognized in Central African Republic, Madagascar, Guinea, and Senegal. Keystone virus was recognized for the first time in New England, and Japanese encephalitis for the first time in the

Philippines. An isolate from a patient in the Netherlands was Colorado tick fever virus. The patient had vacationed in the western United States and returned sick to Holland where he removed a tick from himself. This is an example of long distance transport of a human viral pathogen.

Over 150 strains isolated from mosquitoes in Indonesia were referred by the NAMRU-2 Field Facility in Jakarta. Although these strains are not yet completely identified, initial studies indicate that over half of these are dsRNA viruses, probably orbiviruses. The dsRNA segments were studied by polyacrylamide gel electrophoresis (PAGE). The PAGE patterns indicated that there were multiple genotypes among these isolates. These viruses were isolated in the C6/36 clone of Aedes albopictus cells; they illustrated the power of the PAGE technique in identification of strains which were not mouse-pathogenic, and in some cases did not cause CPE in vertebrate tissue culture. Other similar mosquito cell isolates were studied from China, Hawaii, Thailand, and Israel.

The center was called upon frequently to confirm the identity of viruses used by other researchers. The identity of two strains of SLE virus isolated by U.S. Army researchers in overwintering Culex was confirmed; the identity of Junin vaccine virus was certified; and a plaque-clone of Dhori virus was identified for researchers at the University of Alabama who had shown it to contain 8 segments of RNA. In all, 420 viruses were identified between 1977 and 1983.

Virus classification. The vast majority of arboviruses pertain to 4 major virus families — Togaviridae (genera Alphavirus and Flavivirus), Rhabdoviridae, Reoviridae (genus Orbivirus), and Bunyaviridae (genera Bunyavirus, Nairovirus, Phlebovirus, and Uukuvirus). Reference sera and viruses were produced and distributed for viruses in each of these families. These reagents formed the basis for a collaborative study by plaque reduction neutralization carried out at CDC, Fort Collins and USAMRIID, Fort Detrick to classify the viruses in the genus Flavivirus. A major revision of the family Rhabdoviridae was done by complement fixation, immunofluorescence, and plaque reduction neutralization involving 51 viruses. A similar revision of the genus Phlebovirus was completed with 35 viruses. The finding that Rift Valley fever belonged to this genus had a major impact on the progress of research with this virus. The serological relationships among viruses of the genus Nairovirus were delineated, and these agents were supplied to the Department of Microbiology at the University of Alabama where biochemical studies were done. Another major revision was done in the genus Orbivirus using complement fixation, plaque reduction neutralization, RNA hybridization and PAGE of dsRNA. It was established that the serotype differences within some serogroups represented hybridization differences in only one or two of the 10 genes comprising each virus in the serogroup.

An attempt to place Hantaan virus into one of the existing serogroups of arboviruses was negative, in spite of extensive serological testing, especially among the members of the family Bunyaviridae.

Serologic surveys. Broadly based arbovirus serological surveys were carried out with sera from Brazil, Guam, U.S.A., Colombia, West Irian, Papua, New Guinea, Liberia, Yugoslavia, Greece, China, Ghana, Cameroon, Israel, Sinai, Egypt, Sudan, Australia, and Indonesia. The distribution of

antibody to alphaviruses, flaviviruses, and several hemorrhagic fever viruses such as Lassa, Rift Valley fever, Marburg/Ebola, and Crimean-Congo hemorrhagic fever were determined.

Diagnosis of disease. The outbreak of Rift Valley fever in Egypt was diagnosed. Chikungunya infection was detected in an American working in West Africa, as was Japanese encephalitis in a Canadian exposed in China, eastern encephalitis in a child from Rhode Island, western encephalitis in a teen-ager exposed in the western U.S.A., Tacaribe virus infection in a laboratory worker, LaCrosse encephalitis in a child from Westchester County, N.Y., and Ross River infections in Canadians returning from the Western Pacific. The cause of fevers in Indonesians was determined in a special fever study. In addition, many outbreaks (apparently not of arbovirus origin) were investigated without obtaining a diagnosis.

Development of techniques and rapid diagnosis. The following were investigated or developed: 1) arbovirus attachment to neural and non-neural cells, 2) demonstration of high salt HA with dengue virus, 3) demonstration of HA in mosquito tissues with WEE virus, 4) animal models for demonstrating pathogenicity of bunyavirus reassortant viruses, 5) ELISA for alphaviruses, flaviviruses, and bunyaviruses, 6) Aedes pseudoscutellaris cells for primary isolation of arboviruses in the field, 7) PAGE analysis of dsRNA viruses for classification, 8) trypsinization and mass culture of Rhipicephalus appendiculatus tick cell line, 9) feeding ticks on capillary tubes, 10) high titered JE virus from persistently infected C6/36 cell line, 11) antigen detection ELISA applied to infected mosquitoes, 12) monoclonal antibodies to Rift Valley fever and Crimean-Congo hemorrhagic fever viruses, 13) IgM antibody detection using ELISA, 14) latex beads for rapid antibody and antigen detection, 15) modified Southern blotting to determine genetic relatedness of RNA viruses, and 16) ELISA on filterpaper blood collections.

Collection of low passage arbovirus strains. A large collection of low passage arbovirus strains has been developed and maintained. Priority was given to yellow fever, dengue, chikungunya, western encephalitis, eastern encephalitis, Japanese encephalitis, and other human disease arboviruses. The original (or as close to original as was available) material was passaged once in C6/36 mosquito cells and the progeny lyophilized in aliquots. These were stored and distributed to any and all persons requesting material for study.

Distribution of reagents. Reference antibody and virus was maintained as lyophilized stock for distribution to U.S. military users and to others on a world-wide basis. Since 1977, 4,653 ampoules of arbovirus reagents were distributed to laboratories in more than 40 countries. This total consisted of 1,574 ampoules of virus stock, 1,384 ampoules of virus antigen, and 1,695 ampoules of antibody.

Cell lines were also distributed. These included 51 Aedes albopictus, 6 Aedes aegypti, 1 LLC-MK2, 4 Rhipicephalus, 8 toad, 20 Aedes pseudoscutellaris, 10 Vero, 7 BHK-21, 7 RML-15 and 5 CER lines.

d) Conclusions:

The World Reference Center between 1977 and 1983, maintained an active reference program, both in support of U.S. Navy programs and in support of other national and international agencies and universities. Viruses were identified, arbovirus taxonomy maintained in a competent, structured manner; the world arbovirus collection was curated and increased in numbers and quality; the distribution of arboviruses was determined through serosurvey and isolation of agents; disease outbreaks were diagnosed; new technology was introduced for rapid and early diagnosis; and viruses, cell cultures, and colonized vectors were distributed on a world basis.

e) Major accomplishments:

1. Over 400 viruses were identified, many of them new to science and/or new to a geographic region.
2. The taxonomy of 4 families of viruses was revised.
3. The distribution of arbovirus antibody was determined throughout the world by serosurvey.
4. Rift Valley fever was identified from Egypt and bluetongue virus was identified from Australia; these were medically or economically major events.
5. Techniques for rapid and early diagnosis of arbovirus disease were developed and transferred as technology to users throughout the world.
6. Over 4,000 ampoules of arbovirus reagents were distributed to the U.S. military and other laboratories throughout the world.



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b) Index of annual reports:

Annual report for 1978  
Annual report for 1979  
Annual report for 1980  
Annual report for 1981  
Annual report for 1982  
Annual report for 1983 (submitted to US Army R&D Command)

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The World Reference Center for Arboviruses identified over 400 viruses and revised the taxonomy of Bunyaviridae, <u>Orbivirus</u> , Rhabdoviridae, Arenaviridae, and Togaviridae. Outbreaks were diagnosed such as Rift Valley fever in Egypt in 1977. Rapid and early diagnosis methods were developed including immunofluorescence and ELISA. Some of these utilized monoclonal antibody. Virus reference strains and antibody were distributed world-wide.		

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